Type 2 Diabetes Pharmacotherapy

Adapted from the 2025 ADA Standards of Care in Diabetes

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Healthy lifestyle behaviors, self-management education/support, and social determinants of health should be considered in all patients

First-line pharmacotherapy (**metformin** or other agents) should be selected based upon patient-specific factors
(e.g., glycemic goals, weight goals, comorbidities, tolerability, cost)

Consider **combination pharmacotherapy** at initiation if A1C ≥1.5% above target goal

Consider **early insulin initiation** if A1C >10%, BG ≥300 mg/dL, or symptoms of hyperglycemia
(e.g., polydipsia, polyuria, unexpected weight loss)

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Reassess treatment plan every **3-6 months** and modify, if appropriate

Glycemic Treatment Goals
Must be individualized and periodically reassessed after considering patient-specific characteristics

POPULATION	A1C	PREPRANDIAL	2-HR PPG
Most patients*	<7%	80-130 mg/dL	<180 mg/dL
Certain patients^	<8%	- -	- -

* Stricter goals may be reasonable for certain patients, if achievable without significant hypoglycemia risk
^ e.g., risk of severe hypoglycemia, limited life expectancy, significant comorbidities

Established ASCVD/High Risk, Heart Failure, or Chronic Kidney Disease? — No

Recommended irrespective of A1C or use of metformin

ASCVD
(established or high risk†)

GLP-1 RA or **SGLT2i** with proven CVD benefit

If A1C above target
- On **GLP-1 RA**? Consider adding **SGLT2i** with CVD benefit *(or vice versa)*
- Consider low‡-dose pioglitazone

Heart Failure
(preserved or reduced EF)

SGLT2i (or SGLT1/2i) with proven HF benefit

Or

GLP-1 RA with proven HF benefit in those with symptomatic **HFpEF** and **obesity**

Chronic Kidney Disease
(eGFR <60 mL/min/1.73 m2 or UACR ≥30 mg/g)

Maximally tolerated **ACEi/ARB**

SGLT2i with primary evidence for reducing CKD progression
- May be initiated with eGFR ≥20 mL/min/1.73 m2
- Continue until transplant or dialysis

Or

GLP-1 RA with proven CKD benefit

If A1C above target

On **SGLT2i**? Consider adding **GLP-1 RA** *(or vice versa)*

Additional therapy needed to achieve treatment goals?

† High risk for ASCVD: Typically age ≥55 years plus ≥2 risk factors (e.g., hypertension, obesity, smoking, dyslipidemia, albuminuria)
‡ Avoid use in patients with **heart failure**

CLASS	ASCVD	HEART FAILURE	RENAL
SGLT2is**	**FDA approved CVD benefit:** • canagliflozin • empagliflozin **Neutral:** • bexagliflozin • dapagliflozin • ertugliflozin	**FDA approved HF benefit:** • dapagliflozin • empagliflozin **Evidence for HF benefit:** • canagliflozin • ertugliflozin	**FDA approved renal benefit:** • canagliflozin (DKD) • dapagliflozin (CKD) • empagliflozin (CKD) **Neutral:** • bexagliflozin • ertugliflozin
GLP-1 RAs^^	**FDA approved CVD benefit:** • dulaglutide • liraglutide • semaglutide (SUBQ) **Neutral:** • exenatide ER • semaglutide (oral)	**Evidence for benefit in symptomatic HFpEF and obesity:** • semaglutide (SUBQ)	**Evidence for renal benefit:** • dulaglutide • liraglutide • semaglutide (SUBQ)

FDA labeled indications and evidence for individual agents are subject to frequent change and geographic variability. Last updated 1/2025.

** The ADA recommends sotagliflozin (SGLT1/2 inhibitor) as an option for heart failure benefit. It is not FDA-approved for glycemic management.
^^ Tirzepatide (GIP/GLP-1 RA) is under investigation for cardiorenal benefit.

Select therapies with **adequate efficacy** to achieve and maintain **treatment goals**

Do not combine DPP-4i, GLP-1 RA and/or tirzepatide (GIP/GLP-1 RA)

Glucose-Lowering Efficacy

Very High:
Dulaglutide (high-dose)
Semaglutide
Tirzepatide
Insulin
Combination oral or injectable therapy

High:
GLP-1 RA *(not listed above)*
Metformin
SGLT2i
Sulfonylurea
Pioglitazone

Intermediate:
DPP-4i

Weight-Loss Efficacy

Very High:
Semaglutide
Tirzepatide

High:
Dulaglutide
Liraglutide

Intermediate:
GLP-1 RA *(not listed above)*
SGLT2i

Neutral:
DPP-4i
Metformin

Cost and Access

Consider oral options available in a generic form or at a lower cost, such as:
- Metformin
- Sulfonylurea
- Pioglitazone

Consider insulins that are available at lower cost:
- NPH or regular

Insulin analogs have lower hypoglycemia risk than human insulin (NPH or premixed)

Patient assistance programs may be available for certain brand name medications

Additional therapy needed to achieve treatment goals?

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD):

Consider use of a **GLP-1 RA** or **GIP/GLP-1 RA** in adults with T2DM, MASLD, and overweight/obesity for **weight loss** and potential benefit in metabolic dysfunction-associated steatohepatitis (MASH).

In adults with T2DM and biopsy-proven **MASH** (or those at high risk for clinically significant liver fibrosis), the use of pioglitazone, GLP-1 RA, or GIP/GLP-1 RA is preferred for glucose management due to potential benefits in MASH. Combination therapy (pioglitazone plus GLP-1 RA) may also be considered in these patients.

In patients with T2DM and **decompensated cirrhosis**, insulin therapy is preferred for management of hyperglycemia.

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ASCVD: atherosclerotic cardiovascular disease **CKD:** chronic kidney disease **DKD:** diabetic kidney disease **EF:** ejection fraction **HFpEF:** heart failure with preserved ejection fraction **UACR:** urine albumin-creatinine ratio

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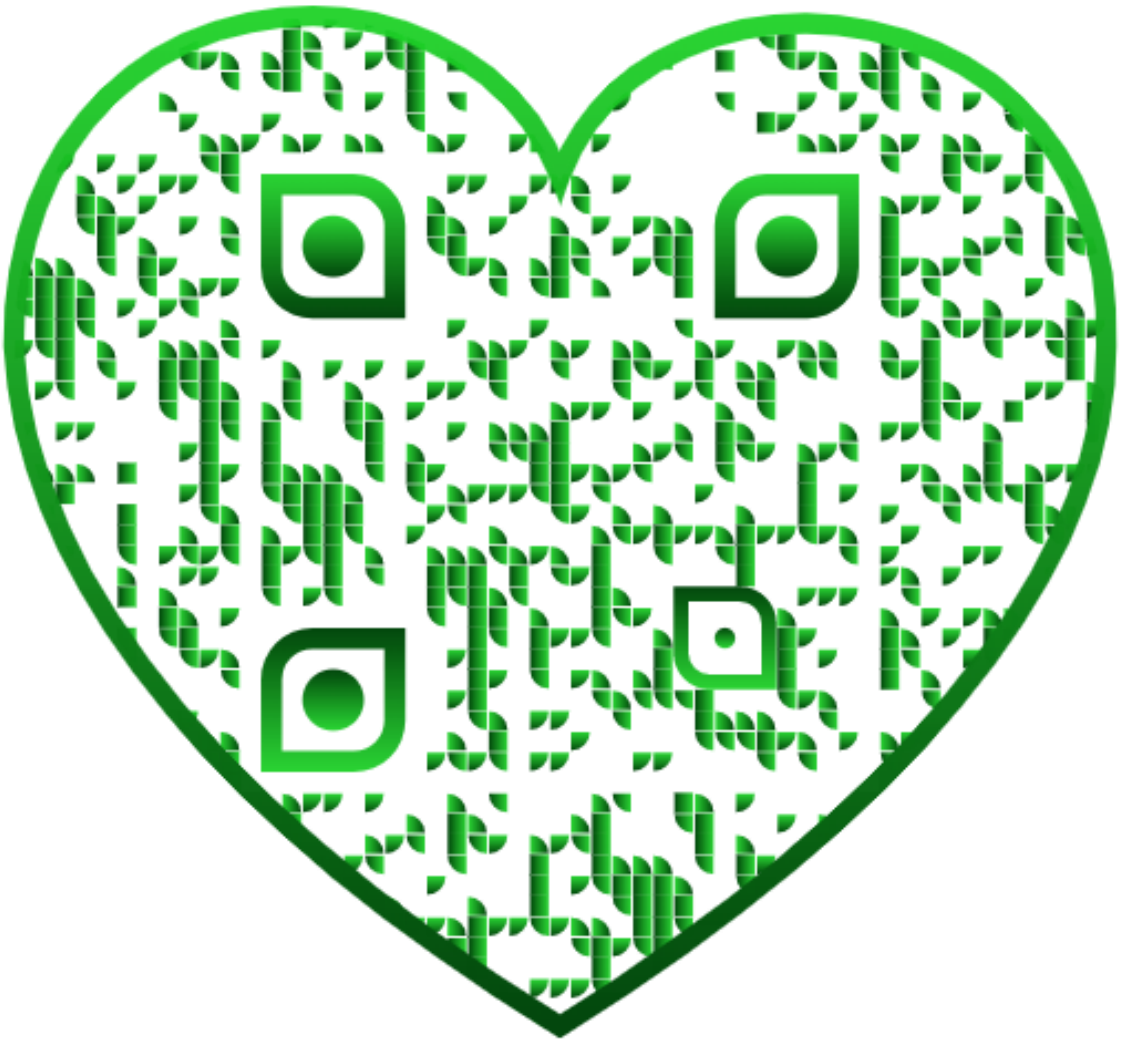

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Comprehensive lifestyle changes and noninsulin agents should generally be considered **prior** to insulin therapy

Consider early insulin initiation if A1C >10%, BG ≥300 mg/dL, or symptoms of hyperglycemia *(e.g., polydipsia, polyuria, unexpected weight loss)*

See Page 1 regarding initial pharmacotherapy use and selection

Insulin Products Chart

Insulin Injection Areas

Reassess treatment plan every **3-6 months** and modify, if appropriate

Injectable therapy needed to lower A1C?

Consider initiating **GLP-1 RA** or **GIP/GLP-1 RA** in most patients **prior** to insulin

Titrate to maintenance dose

- Already on **GLP-1 RA** or **GIP/GLP-1 RA**?
- GLP-1 RA or GIP/GLP-1 RA **not appropriate**?
- **Insulin preferred**?

Add **basal insulin analog** or **bedtime NPH** based upon patient-specific factors and cost

START: 10 units daily **or** 0.1 to 0.2 units/kg daily

TITRATE to target fasting plasma glucose (FPG):

- Follow an evidence-based algorithm (e.g., increase by 2 units every 3 days)
- Titrate at a rate to minimize hypoglycemia risk
- If hypoglycemia occurs for no clear reason, decrease dose by 10 to 20%

Assess basal insulin dose adequacy and evaluate for overbasalization

Evaluate for clinical signs of overbasalization or need for adjunctive therapy:

- Elevated bedtime-to-morning or pre-to-postprandial differential
- Hypoglycemia (aware/unaware)
- High glycemic variability

If A1C is above target

On bedtime NPH? Consider conversion to twice-daily dosing

<u>One possible approach</u>:

START:

- Total dose = 80% of current
- 2/3rd given in the morning
- 1/3rd given at bedtime

Titrate based on the individual's needs

If A1C is above target

Add prandial insulin

Usually start with **one dose** with the largest meal (or meal with greatest PPG excursion). Prandial insulin can be dosed individually or mixed with NPH as appropriate.

START:

- 4 units daily or 10% of basal dose
- If A1C <8%, consider **decreasing** basal dose by 4 units daily or by 10% of basal dose

TITRATION:

- **Increase** dose by 1 to 2 units or 10 to 15% twice weekly
- If hypoglycemia occurs for no clear reason, **decrease** dose by 10 to 20%

If A1C is above target

Consider twice-daily premixed insulin

START:

- Typically unit per unit at same total insulin dose
- May require adjustment for the individual's needs

Titrate based on the individual's needs

Stepwise additional prandial doses

(i.e., 2, then 3 doses daily)

Full basal-bolus regimen

(i.e., basal insulin plus bolus insulin with each meal)

Consider self-mixed/split insulin regimen

May adjust NPH and short-/rapid-acting insulins separately

START:

- Total NPH dose = 80% of current NPH dose
- 2/3rd given before breakfast
- 1/3rd given before dinner
- Add 4 units of short-/rapid-acting insulin to each injection or 10% of reduced NPH dose

Titrate components of regimen based on the individual's needs

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